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Chromium hydride intermediates in the case of *cine* and *tele-meta* nucleophilic aromatic substitution on arenetricarbonylchromium complexes

Vanessa Gagliardini, Valérie Onnikian, Françoise Rose-Munch, Eric Rose *

Laboratoire de Synthèse Organique et Organométallique, URA CNRS 408, Université P. et M. Curie, Case 181, 4 place Jussieu, Tour 44, 75252 Paris, Cedex 05, France

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Abstract

Treatment of (η^6-1,2,3-trimethoxybenzene) and (η^6-veratrole) tricarbonylchromium complexes **1** and **5** with a carbanion in THF and then with acid affords as the major products 4-substituted (η^6-veratrole) and 3-substituted (η^6-anisole) tricarbonylchromium complexes according to *tele-meta* and *cine* nucleophilic aromatic substitutions, respectively.

Keywords: Nucleophilic aromatic substitution; Chromium complexes; Arene complexes; Carbonyl complexes; Hydride complexes

1. Introduction

(η^6-Arene)tricarbonylchromium complexes play an important role in organic synthesis [1]. We have recently described their use not only in asymmetric formation of (η^6-benzaldehyde)tricarbonylchromium complexes [2] but also in new methods of cleavage of aromatic carbon–oxygen [3], carbon–halogen [4] and carbon–nitrogen [5] bonds of alkoxy, halogeno and dialkylamino (η^6-arene)tricarbonylchromium complexes via *cine* [6] and *tele-meta* [7] nucleophilic aromatic substitution reactions. Indeed, our research is mainly oriented in the mechanism study of the addition of nucleophiles and electrophiles to substituted (η^6-arene)tricarbonylchromium complexes. Herein, we report the study of the carbanion addition to the (1,2,3-trimethoxybenzene)tricarbonylchromium complex in order to prepare veratrole derivatives substituted at the C4 carbon because they can be useful for the synthesis of dopamine derivatives. We extended our work to the synthesis of *meta*-substituted anisole derivatives in the case of the reactivity of the veratrole complex.

2. Experimental

All reactions were carried out under a dry nitrogen atmosphere. The (η^6-arene)tricarbonylchromium complexes were generally stable in air for a long period of time in the solid state. Nevertheless, many derivatives were found to decompose fast in THF solutions on exposure to air. Consequently, all experiments were always protected from exposure to light and oxygen. Tetrahydrofuran (THF) and di-n-butylether (n-Bu_2O) were dried over sodium benzoketyl under dry nitrogen atmosphere and distilled just before use. Before performing NMR experiments, NMR solvents and tubes were purged with dry nitrogen to remove oxygen. ^1H and ^{13}C NMR spectra were acquired on a Brücker AC 200 and 400 spectrometer and chemical shifts were reported in ppm downfield of Me_4Si. ^1H NMR spectra were referenced against the residual ^1H impurity of the deuterated solvent (δ (ppm) 7.15 (C_6D_6); 1.85, 3.75 (C_4D_8O)), and ^{13}C NMR spectra were referenced against the ^{13}C resonance of the solvent (δ 128.0 (C_6D_6); 25.3, 67.4 (C_4D_8O)). IR spectra were performed on a Perkin-Elmer 1420. Mass spectra were obtained on a Nermag R 30-40 spectrometer, with a direct insert source, using the electronic impact (EI) method. Elemental analyses (reported in % mass) were performed by 'Le Service de Microanalyses de l'Université P. et M. Curie'.

2.1. Tricarbonyl(η^6-1,2,3-trimethoxybenzene)chromium (1)

1,2,3-Trimethoxybenzene (12 g; 71.3 mmol), $Cr(CO)_6$ (10.3 g; 47.1 mmol), dry THF (10 ml) and dry di-n-butylether (90 ml) were heated under nitrogen. Reflux was carried out for 5 days. The yellow solution was filtered on celite and

* Corresponding author. E-mail: rose@ccr.jussieu.fr

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the solvents evaporated under reduced pressure. The residue was chromatographed on a 15–40 μm silica gel column. 13.7 g (45 mmol) of complex **1** were obtained in 96% yield. Lit. (yield) = 22% [14].

1: *Anal.* Calc. for $C_{12}H_{12}CrO_6$: C, 47.37; H, 3.97. Found: C, 47.66; H, 3.91%. IR (CCl_4, cm^{-1}): ν(CO) 1965, 1888. ^1H NMR ($CDCl_3$): δ 5.42 (t, $J=7$, H^5), 4.75 (d, $J=7$, $H^{4,6}$), 3.90 (s, OCH_3 C^2), 3.82 (s, OCH_3 $C^{1,3}$). ^{13}C NMR ($CDCl_3$): δ 233.69 (Cr–*C*O), 139.89 ($C^{1,3}$), 121.36 (C^2), 89.90 (C^5), 68.86 ($C^{4,6}$), 66.52 (OCH_3 C^2), 56.33 (OCH_3 $C^{1,3}$).

2.2. Tricarbonyl(η⁶-veratrole)chromium (5)

Prepared as before. Yield = 49% [14]; yield = 91% [10g].

5: *Anal.* Calc. for $C_{11}H_{10}CrO_5$: C, 48.17; H, 3.67. Found: C, 48.28; H, 3.93%. IR (CCl_4, cm^{-1}): ν(CO) 1970, 1895. ^1H NMR ($CDCl_3$): δ 5.30 (dd, $J=6$, 2, $H^{3,6}$), 5.06 (dd, $J=6$, 2, $H^{4,5}$), 3.79 (s, OCH_3 $C^{1,2}$). ^{13}C NMR ($CDCl_3$): δ 233.89 (Cr–*C*O), 133.33 ($C^{1,2}$), 87.34 ($C^{4,5}$), 78.52 ($C^{3,6}$), 57.34 (OCH_3).

2.3. Tele-meta nucleophilic aromatic substitution

n-BuLi (1.6 M in hexane, 2 ml, 2.5 mmol) was added to diisopropylamine (350 μl, 2.5 mmol) in THF (10 ml) at −78°C under N_2. After 10 min, CH_3CN (131 μl, 2.5 mmol) was added and the solution stirred for 15 min at −78°C. A THF (10 ml) solution of complex **1** (304 mg, 1 mmol) at −78°C was transferred via a canula to the $LiCH_2CN$ solution. After 1 h at −78°C, the yellow solution was transferred in a CF_3CO_2H solution (231 μl, 3 mmol) in THF (5 ml) at −78°C. The orange–red solution was stirred for 30 min at −78°C and became yellow at r.t. The solution was extracted with ether/H_2O–KOH. The organic phase was washed with H_2O and brine. After filtration over $MgSO_4$, the solvents were evaporated under reduced pressure. The yellow residue was purified on a 15–40 μm silica gel chromatography column with a 30:100 mixture of ethyl acetate/petroleum ether giving a first complex **3a** (22%, 71 mg, 0.2 mmol) and a second yellow complex **2a** with a 35:100 mixture of ethyl acetate/petroleum ether (42%, 133 mg, 0.4 mmol).

2a: *Anal.* Calc. for $C_{13}H_{11}CrNO_5$: C, 49.85; H, 3.53; N, 4.47. Found: C, 49.77; H, 3.91; N, 4.06%. IR (CCl_4, cm^{-1}): ν(CO) 1965, 1895; ν(CN) 2320. ^1H NMR ($CDCl_3$): δ 5.34 (d, $J=7$, H^5), 5.24 (s, H^2), 5.03 (d, $J=7$, H^6), 3.83 (s, OCH_3 C^3), 3.78 (s, OCH_3 C^4), 3.51 (m, CH_2CN). ^{13}C NMR ($CDCl_3$): δ 232.24 (Cr–*C*O), 131.25 (C^3), 131.57 (C^4), 115.75 (*C*N), 94.75 (C^1), 85.17 (C^6), 77.93 (C^5), 77.23 (C^2), 57.52, 57.10 (OCH_3 $C^{3,4}$), 21.00 (CH_2CN).

3a: *Anal.* Calc. for $C_{13}H_{11}CrNO_5$: C, 49.85; H, 3.53; N, 4.47. Found: C, 49.34; H, 3.74; N, 4.66%. IR (CCl_4, cm^{-1}): ν(CO) 1965, 1895; ν(CN) 2320. ^1H NMR ($CDCl_3$): δ 5.39 (t, $J=6$, H^5), 5.08 (d, $J=6$, $H^{4\text{ or }6}$), 4.94 (d, $J=6$, $H^{6\text{ or }4}$), 3.91 (s, OCH_3 C^3), 3.86 (s, OCH_3 C^2), 3.75 (d, $J=18$, H_a CH_aH_bCN), 3.52 (d, $J=18$, H_b CH_aH_bCN). ^{13}C NMR ($CDCl_3$): δ 232.63 (Cr–*C*O), 136.41 (C^3), 127.37 (C^2), 116.23 (*C*N), 100.14 (C^1), 90.23 (C^5), 83.88 (C^6), 74.34 (C^4), 65.29, 56.45 (OCH_3 $C^{2,3}$), 19.43 (CH_2CN).

Using the same experimental procedure, complexes **2b** and **3b** were obtained. **2b** and **3b** are mixtures of two diastereoisomers **2b₁** and **2b₂** (separated by chromatography column, 75%, ratio 38:72), and **3b₁** and **3b₂** (5%).

2b₁: *Anal.* Calc. for $C_{14}H_{13}CrNO_5$: C, 51.38; H, 4.00; N, 4.28. Found: C, 51.46; H, 4.01; N, 4.35%. IR ($CHCl_3$, cm^{-1}): ν(CO) 1965, 1890; ν(CN) 2240. ^1H NMR (d_6-acetone): δ 5.95 (d, $J=2$, H^2), 5.84 (d, $J=7$, H^5), 5.53 (dd, $J=7$, 2, H^6), 3.99 (q, $J=7$, *C*HCN), 3.88, 3.84 (s, 2OCH_3 $C^{3,4}$), 1.66 (d, $J=7$, CH_3CN). ^{13}C NMR (d_6-acetone): δ 232.28 (Cr–*C*O), 133.02 (C^3), 132.36 (C^4), 119.28 (*C*N), 102.64 (C^1), 86.32 (C^6), 78.82 (C^2), 78.06 (C^5), 56.19, 56.09 (OCH_3 $C^{3,4}$), 28.75 (*C*HCN), 19.21 (CH_3CN).

2b₂: *Anal.* Calc. for $C_{14}H_{13}CrNO_5$: C, 51.38; H, 4.00; N, 4.28. Found: C, 51.48; H, 4.14; N, 4.36%. IR ($CHCl_3$, cm^{-1}): ν(CO) 1965, 1885; ν(CN) 2235. ^1H NMR (d_6-acetone): δ 5.95 (d, $J=2$, H^2), 5.86 (d, $J=7$, H^5), 5.48 (dd, $J=7$, 2, H^6), 4.00 (q, $J=7$, *C*HCN), 3.83, 3.82 (s, 2 OCH_3 $C^{1,2}$), 1.68 (d, $J=7$, CH_3CN). ^{13}C NMR (d_6-acetone): δ 232.25 (Cr–*C*O), 133.65 (C^3), 133.42 (C^4), 119.65 (*C*N), 103.66 (C^1), 85.66 (C^6), 79.43 (C^2), 78.73 (C^5), 56.77, 56.67 (OCH_3 $C^{3,4}$), 30.30 (*C*HCN), 21.24 (CH_3CN).

3b mixture, $C_{14}H_{13}CrNO_5$: ^1H NMR ($CDCl_3$): δ 5.47, 5.36 (t, $J=6$, H^5), 5.20, 5.11, 5.05, 4.85 (d, $J=6$, $H^{6,4}$), 3.94, 3.90, 3.89, 3.87 (s, OCH_3 $C^{2,3}$), 3.80 (m, *C*HCN), 1.70, 1.66 (d, CH_3CN).

Using the same experimental procedure, complex **2c** is obtained (98%).

2c: *Anal.* Calc. for $C_{15}H_{15}CrNO_5$: C, 52.79; H, 4.43; N, 4.10. Found: C, 52.66; H, 4.55; N, 4.08%. IR ($CHCl_3$, cm^{-1}): ν(CO) 1965, 1890; ν(CN) 2225. ^1H NMR (d_6-acetone): δ 5.95 (d, $J=1$, H^3), 5.76 (d, $J=7$, H^5), 5.63 (dd, $J=7$, 1, H^6), 3.86, 3.85 (s, OCH_3 $C^{1,2}$), 1.79, 1.73 (s, CH_3CN). ^1H NMR ($CDCl_3$): δ 5.53 (s, H^3), 5.20 (s, $H^{5,6}$), 3.83, 3.81 (s, OCH_3 $C^{3,4}$), 1.70, 1.66 (s, CH_3CN). ^{13}C NMR ($CDCl_3$): δ 231.41 (Cr–*C*O), 132.83 (C^2), 129.74 (C^1), 121.29 (*C*N), 105.01 (C^4), 84.02 (C^5), 76.99 (C^3), 74.33 (C^6), 57.00, 56.03 (OCH_3 $C^{1,2}$), 35.08 (*C*CN), 28.80, 27.41 (CH_3CN).

2.4. Deuteration of complex 1

Addition of n-BuLi (1.6 M in hexane, 4 ml, 6.7 mmol) to a THF (8 ml) solution of complex **1** (204 mg, 0.67 mmol) at −78°C and then CF_3CO_2D (1 ml, 13 mmol) gives a 60:40 ratio of mono- and di-deuterated complexes **1D₁** and **1D₂** (Eq. (2)). The reaction mixture treated again with n-BuLi and CF_3CO_2D affords a first non-polar by-product **4** and then complexes **1D₁** and **1D₂** in the ratio 1:9. Resonances of protons H4,6 at 4.75 ppm almost disappear in the ^1H NMR spectrum of this mixture. Addition of $LiCMe_2CN$ and then CF_3CO_2H yields as the major product complex **2c-D₂** (Eq. (3)) whose ^1H NMR (acetone-d_6) spectrum shows no resonances at 5.95 and 5.63 ppm.

4, $C_{15}H_{16}CrD_2O_5$: MS: *m/z* 332 ($M^{\cdot+}$), 248 ($M^{\cdot+}-3CO$). ^1H NMR ($CDCl_3$): δ 5.37 (s, H^5), 3.85, 3.80 (s, OCH_3 $C^{1,2}$), 2.77 (m, $-CH_aH_{a'}C_3H_7$), 2.23 (m, $-CH_aH_{a'}C_3H_7$), 1.44 (m, $-CH_2CH_2CH_3$), 0.92 (t, $J=8$, $-CH_3$). ^{13}C NMR ($CDCl_3$): δ 232.85 (Cr–*C*O), 136.58, 127.72 ($C^{1,2}$), 112.57 (C^3), 90.82 (C^5), 83.48 (t, $J=26$, *C*–D $C^{4\text{ or }6}$), 71.87 (t, $J=26$, *C*–D $C^{6\text{ or }4}$), 64.85, 59.58 (OCH_3 $C^{1,2}$), 31.43 (CH_2), 29.20 ($CH_aH_{a'}$), 21.50 (CH_2), 12.84 (CH_3).

1D$_1$, $C_{12}H_{11}CrDO_6$: ^1H NMR ($CDCl_3$): δ 5.42 (d, $J=7$, H^5), 4.75 (d, $J=7$, H^6), 3.90 (s, OCH_3 C^2), 3.82 (s, OCH_3 $C^{1,3}$).

1D$_2$, $C_{12}H_{10}CrD_2O_6$: MS: *m/z* 306 ($M^{\cdot+}$), 250 ($M^{\cdot+}-2CO$), 222 ($M^{\cdot+}-3CO$). IR ($CHCl_3$, cm^{-1}): ν(CO) 1960, 1875. ^1H NMR ($CDCl_3$): δ 5.42 (s, H^5), 3.90 (s, OCH_3 C^2), 3.82 (s, OCH_3 $C^{1,3}$). ^{13}C NMR ($CDCl_3$): δ 233.89 (Cr–*C*O), 139.89 ($C^{1,3}$), 121.36 (C^2), 89.90 (C^5), 68.86 (t, $J=26$, *C*–D $C^{4,6}$), 66.52 (OCH_3 C^2), 56.33 (OCH_3 $C^{1,3}$).

2c-D$_2$, $C_{15}H_{13}CrND_2O_5$: IR ($CHCl_3$, cm^{-1}): ν(CO) 1965, 1890; ν(CN) 2225. ^1H NMR (d_6-acetone): δ 5.76 (s, H^6), 3.86, 3.85 (s, OCH_3 $C^{1,2}$), 1.79, 1.73 (s, CH_3CN). ^1H NMR ($CDCl_3$): δ 5.20 (s, H^6), 3.83, 3.81 (s, OCH_3 $C^{1,2}$), 1.70, 1.66 (s, CH_3CN). ^{13}C NMR ($CDCl_3$): δ 231.41 (Cr–*C*O), 132.83 (C^2), 129.74 (C^1), 121.29 (*C*N), 105.01 (C^4), 84.02 (t, $J=26$, *C*–D C^5), 76.99 (t, $J=26$, *C*–D C^3), 74.33 (C^6), 57.00, 56.03 (OCH_3 $C^{2,1}$), 35.08 (*C*CN), 28.80, 27.41 (CH_3CN).

2.5. Cine nucleophilic aromatic substitution

n-BuLi (1.6 M in hexane, 375 μl, 0.6 mmol) was added to diisopropylamine (84 μl, 0.6 mmol) in THF (5 ml) at −78°C under N_2. After 10 min, CH_3CN (31 μl, 0.6 mmol) was added and the solution stirred for 15 min at −78°C. A THF (5 ml) solution of complex **5** (137 mg, 0.5 mmol) at −78°C was transferred via a canula to the $LiCH_2CN$ solution. After 30 min at −78°C and 30 min at −40°C, the yellow solution was transferred in a CF_3CO_2H solution (113 μl, 1.5 mmol) in THF (3 ml) at −78°C. The orange–red solution was stirred for 30 min at −78°C and became yellow at r.t. (15 h). The solution was extracted with ether/H_2O–KOH. The organic phase was washed with H_2O and brine. After filtration over $MgSO_4$, the solvents were evaporated under reduced pressure. The yellow residue was purified on a 15–40 μm silica gel chromatography column giving a first complex **7a** (in mixture with complex **5**) with a 40:100 mixture of ether and petroleum ether and a second complex **6a** with a 80:100 mixture of ether and petroleum ether (**6a**: 47%, 66 mg, 0.23 mmol).

7a, $C_{12}H_9CrNO_4$: ^1H NMR ($CDCl_3$): δ 5.70 (d, $J=6$, H^6), 5.51 (t, $J=6$, H^4), 5.08 (d, $J=6$, H^3), 4.93 (t, $J=6$, H^5), 3.81 (s, OCH_3 C^2), 3.67 (s, CH_2CN).

6a: *Anal.* Calc. for $C_{12}H_9CrNO_4$: C, 50.85; H, 3.18. Found: C, 50.84; H, 3.12%. IR (CCl_4, cm^{-1}): ν(CO) 1975, 1955, 1905; ν(CN) 2235. ^1H NMR ($CDCl_3$): δ 5.60 (t, $J=6$, H^5), 5.08 (m, $H^{2,6}$), 4.85 (d, $J=6$, H^4), 3.74 (s, OCH_3 C^3), 3.62 (s, CH_2CN). ^1H NMR (d_6-acetone): δ 4.88 (t, $J=6$, H^5), 4.47 (s, H^2), 4.37 (d, $J=6$, H^6), 4.17 (d, $J=6$, H^4), 2.89 (s, CH_2CN), 2.79 (s, OCH_3 C^3). ^{13}C NMR ($CDCl_3$): δ 196.67 (Cr–*C*O), 143.33 (C^3), 120.60 (*C*N), 102.12 (C^1), 94.15 (C^5), 84.22 (C^4), 77.24 (C^2), 76.10 (C^6), 55.55, (OCH_3 C^3), 23.09 (CH_2CN).

Using the same experimental procedure, complexes **6b** were obtained. **6b** is a mixture of two diastereoisomers **6b$_1$** and **6b$_2$** which cannot be separated on a chromatography column (67%, ratio 67:33).

6b mixture, $C_{13}H_{11}CrNO_4$: IR (nujol, cm^{-1}): ν(CO) 1975, 1955, 1945 (CO); ν(CN) 2240. ^1H NMR ($CDCl_3$): δ 5.59 (m, H^5, $H^{5'}$), 5.24 (s, H^2, $H^{2'}$), 5.03 (m, H^6, $H^{6'}$, H^4, $H^{4'}$), 3.76 (m, $-CHCN$, $-CH'CN$), 3.74, 3.72 (2s, OCH_3, OCH_3, C^3), 1.70 (d, $J=7$, CH_3CN, CH'_3CN). ^1H NMR (C_6D_6): δ 4.79, 4.24 (s, H^2, $H^{2'}$), 4.56 (m, H^5, $H^{5'}$), 4.32, 4.20 (d, $J=7$, H^6, $H^{6'}$), 4.07, 3.67 (d, $J=7$, H^4, $H^{4'}$), 3.22, 2.86 (s, OCH_3, OCH'_3 C^3), 3.00, 2.70 (q, $J=7$, *C*HCN, *C*H'CN), 0.99, 0.80 (d, $J=7$, CH_3CN, CH'_3CN). ^{13}C NMR (C_6D_6): δ 233.61 (Cr–*C*O), 143.47, 143.23 (C^3), 122.24, 121.94 (*C*N), 110.59, 110.30 (C^1), 94.84 (C^5), 83.93, 77.27 (C^4), 83.33, 75.94 (C^6), 76.97, 76.67 (C^2), 55.15, 54.94 (OCH_3 C^3), 31.52, 30.85 (*C*HCN), 18.61, 20.30 (CH_3CN).

Using the same experimental procedure, complexes **6c** (54%) and **7c** (2%) were obtained.

6c: *Anal.* Calc. for $C_{14}H_{13}CrNO_4$: C, 53.98; H, 4.18; N, 4.50. Found: C, 54.02; H, 4.25; N, 4.55%. IR (nujol, cm^{-1}): ν(CO) 1950, 1885, 1850; ν(CN) 2235. ^1H NMR ($CDCl_3$): δ 5.56 (t, $J=7$, H^5), 5.20 (s, H^2), 5.11 (dd, $J=7$, 2, H^6), 4.97 (dd, $J=7$, 2, H^4), 3.73, (s, OCH_3 C^3), 1.75, 1.73 (s, CH_3CN). ^{13}C NMR ($CDCl_3$): δ 232.09 (Cr–*C*O), 142.62 (C^3), 122.35 (*C*N), 114.80 (C^1), 93.64 (C^5), 82.63 (C^4), 76.50 (C^6), 76.18 (C^2), 55.95 (OCH_3 C^3), 37.06 (*C*CN), 29.04, 27.41 (CH_3CN).

7c, $C_{14}H_{13}CrNO_4$: ^1H NMR ($CDCl_3$): δ 5.72 (d, $J=7$, $H^{3,5}$), 5.05 (d, $J=7$, $H^{2,6}$), 3.84, (s, OCH_3 C^3), 1.67 (s, CH_3CN).

3. Results and discussion

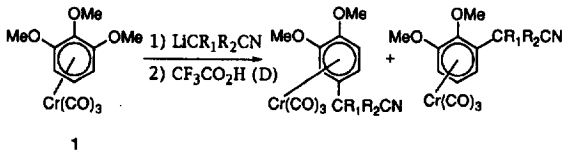
3.1. Reactivity of (η^6-1,2,3-trimethoxybenzene)-tricarbonylchromium (1)

Treatment of the tricarbonyl(η^6-1,2,3-trimethoxybenzene)chromium complex **1** with $LiCH_2CN$ (2.5 equiv.) in THF (−78°C, 30 min) and then with CF_3CO_2H (3 equiv.; −78°C to r.t., 30 min) leads to a mixture of two products **2a** and **3a**. (3,4- and 2,3-Dimethoxy-phenyl)-acetonitrile tricarbonylchromium **2a** and **3a** are isolated after silica gel chromatography column and recrystallisation in 42% and 22% yields, respectively (Eq. (1)).

Treatment of complex **1** with LiCHMeCN (1.1 equiv.) in THF (−78°C, 30 min) gives, after adding CF_3CO_2H (5 equiv.; −78°C to r.t., 30 min), 2-(3,4- and 2,3-dimethoxy-

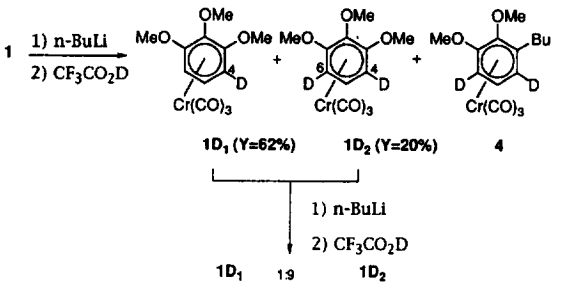
phenyl)-propionitrile tricarbonylchromium **2b** and **3b** which are recovered under the same conditions in 75% and 5% yields, respectively. Complexes **2b** and **3b** are a mixure of two diastereoisomers. These diastereoisomers are easily separated by column chromatography in the case of **2b** (38/72 ratio, Eq. (1)).

Treatment of complex **1** with $LiCMe_2CN$ (1.1 equiv.) in THF (−78°C, 30 min) and then with CF_3CO_2H (5 equiv.; −78°C to r.t., 30 min) affords 2-(3,4-dimethoxy-phenyl)-2-methyl-propionitrile tricarbonyl chromium complex **2c** in 98% yield (Eq. (1)). It is worth noting that the same reactions after CF_3CO_2D treatment, give these complexes without incorporation of deuterium.



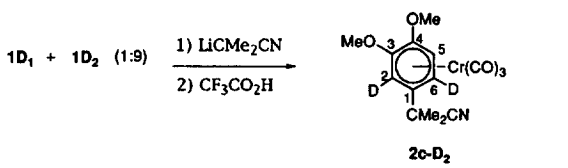
(1)

In order to prove the mechanism of these reactions, we prepared labelled complexes. Addition of n-BuLi (5 equiv.) and CF_3CO_2D (10 equiv.) to complex **1** gives a mixture of 1,2,3-trimethoxy(benzene)tricarbonylchromium complex $\mathbf{1D_1}$ mono-deuterated at the C4 carbon and $\mathbf{1D_2}$ di-deuterated at the C4 and C6 carbons in 62% and 20% yields, respectively. Repeating this reaction, starting from the **1D1** and **1D2** mixture, it is possible to obtain $\mathbf{1D_1}$ and $\mathbf{1D_2}$ in a ratio of 10:90 (Eq. (2)).

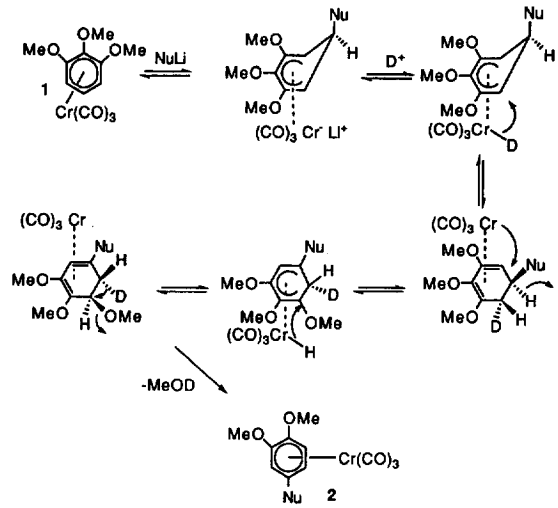


(2)

Treatment of this mixture with isobutyronitrile carbanion and CF_3CO_2H yields complex $\mathbf{2c\text{-}D_2}$ whose ^1H NMR spectrum clearly shows the disappearance of the H_2 and H_6 proton signals at 5.03 and 5.24 ppm with respect to **2c** (Eq. (3)). These experiments are in good agreement with a *tele-meta* nucleophilic aromatic substitution [7] (Scheme 1). The mechanism involves chromium-hydride (deuteride) and (η^4-cyclohexadiene) complexes and will be discussed in more detail in the case of complex **5** (see Scheme 3).



(3)



Scheme 1. Mechanism of a *tele-meta* S_NAr in the case of complex **1**.

It is worth noting the good regioselectivity of the addition of stabilised nucleophiles to the C5 carbon of complex **1**. Indeed, in the case of the tertiary carbanion $LiCMe_2CN$, no other regioisomer is detected by ^1H NMR, only complex **2c** is isolated. The 4-isomers **2a** and **2b** are also the major isomers by addition of $LiCH_2CN$ and LiCHMeCN. This regioselectivity could find interesting applications in the case of the preparation of dopamine derivatives. These 1,2,4-substituted arenes cannot be obtained by adding a nucleophile to the veratrole tricarbonylchromium complex because the addition of stabilised carbanions at low temperature occurs mainly on the C3 carbon [8]. Complexes **3a** and **3b** are obtained by *ipso* substitution of a methoxy group at the carbon C1 by $LiCH_2CN$ and LiCHMeCN. The X-ray structure of complex **1** showed that the C1, C3 and C5 carbons are eclipsed by the $Cr(CO)_3$ tripod according to the conformer **1A** (Fig. 1) [9].

Furthermore, complex **1** can be described in solution by an equilibrium of two conformers **1A** and **1B** (Scheme 2) [10] and the population x of the major conformer can be calculated [10d]. Using the simple equation $\delta_n - \delta_{n-1} = (2x-1)\Delta\delta_{max}$, we can deduce the value x of the conformer

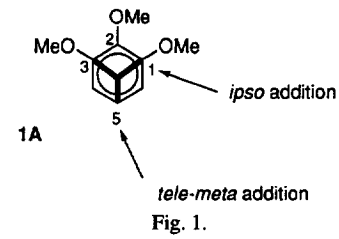
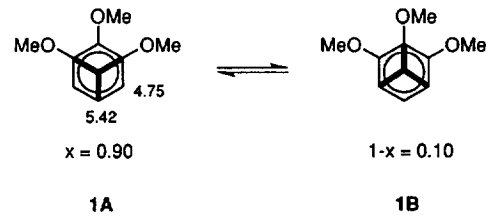


Fig. 1.



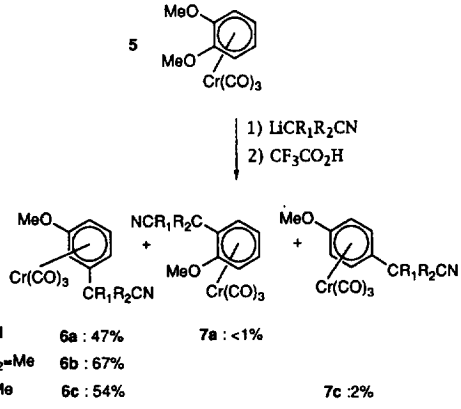
Scheme 2. Equilibrium of two conformers.

eclipsing the C_5 carbon: $5.42-4.75=(2x-1)0.84$; $x=$ 90%. Carbons C1, C3 and C5 which are eclipsed by a Cr–CO bond of conformer **1A** are more electrophilic than carbons C2, C4 and C6 [8b]. It has been shown that in most cases, addition of stabilised carbanions at low temperatures occurs under kinetic control [1k,10e,10g,13] and we have concluded that addition of these nucleophiles takes place on the carbons eclipsed by a chromium carbonyl bond of the major isomer. It has been also shown that the hydrogen eclipsed by a Cr–CO bond of the major conformer resonates in most cases at the lowest field and that the shielding $\delta(H_{i,\text{ free arene}})-\delta(H_{i,\text{ complex}})$ of the eclipsed proton H_i due to the complexation is the smallest [10e,g].

The minor by-product **4** is isolated when the mixture of $\mathbf{1D_1}$ and $\mathbf{1D_2}$ is treated with n-BuLi (Eq. (2)). This corresponds to a 3-butyl, 4,6-dideuterio, veratrole tricarbonylchromium complex characterised by different spectroscopies (see Section 2). Formation of **4** can be interpreted by an *ipso* addition of n-BuLi to the carbon bearing the methoxy group [11].

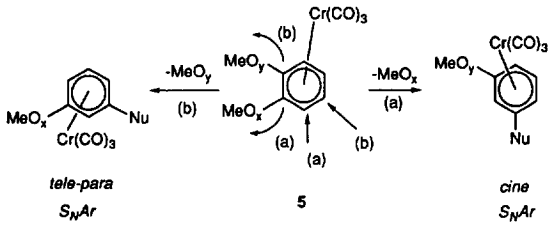
3.2. Reactivity of (η^6-veratrole)tricarbonylchromium (5)

Treatment of veratrole complex **5** with $LiCH_2CN$ (1.2 equiv.) in THF (-78°C, 30 min; -40°C, 30 min) and then with CF_3CO_2H (3 equiv.; -78°C, 30 min; r.t., 15 h) leads to the formation of (3-methoxy-phenyl)-acetonitrile tricarbonylchromium **6a** in 47% yield (Eq. (4)). Complex **7a** can be detected but the yield is lower than 1%.



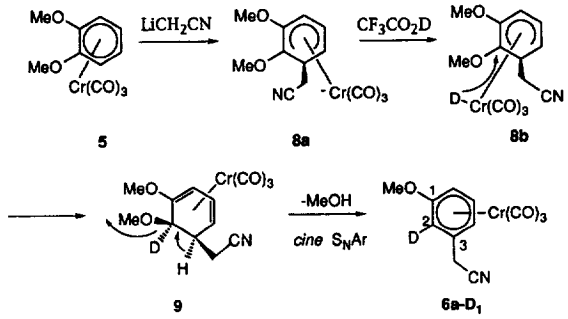
(4)

This experiment could not ascertain whether the carbanion adds to the carbon *ortho* to the methoxy leaving group OMe_x (*cine* S_NAr, path a) or to the carbon *para* to the methoxy leaving group OMe_y (*tele-para* S_NAr, path b) because in each case a *meta*-disubstituted complex is obtained (Eq. (5)).



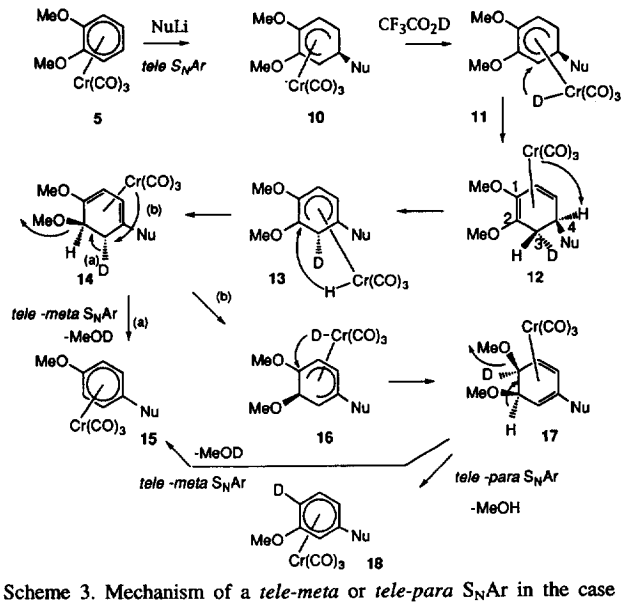
(5)

Consequently, we undertook the study of the reaction of complex **5** with the same carbanion and with CF_3CO_2D. The ^1H NMR spectrum clearly shows that the H_2 proton integration of complex **6a** has diminished significantly, in good agreement with the formation of complex **6a-D1** according to a *cine* S_NAr (Eq. (6)).

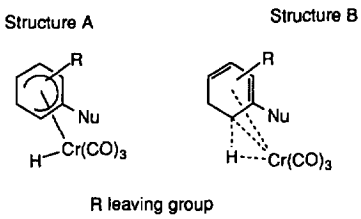


(6)

Indeed, addition of a nucleophile at the C4 carbon gives the anionic (η^5-cyclohexadienyl)tricarbonylchromium complex **10** (Scheme 3). Treatment with CF_3CO_2D can yield the chromium deuteride **11**. Reductive elimination can afford the (η^4-cyclohexadiene)tricarbonylchromium **12** with an *endo*-deuteride at the C3 carbon. Oxidative addition of the *endo*-hydrogen at the C4 carbon gives a new chromium hydride **13**. Hydride can migrate on the C2 carbon. If the new (η^4-cyclohexadiene) **14** isomer eliminates MeOD (*tele-meta* S_NAr), a *para*-disubstituted complex **15** could be obtained with no deuterium labelling. Oxidative addition of the *endo*-deuteride at the C3 carbon (of complex **14**) yields a complex with a chromium–deuteride bond **16**. The (η^4-cyclohexadiene)tricarbonylchromium **17** can be obtained after migration of the deuteride. Elimination of MeOH could afford complex **18** (*tele-para* S_NAr) labelled at the carbon *para* to the nucleophilic group in the case of $Nu=CH_2CN$. The formation of



Scheme 3. Mechanism of a *tele-meta* or *tele-para* S_NAr in the case of complex **5**.



Scheme 4. Possible structures of complexes **11**, **13** and **16**.

this complex has never been observed. So the addition of $LiCH_2CN$ occurs at the C3 carbon of complex **5** and the OMe group at the C2 carbon is eliminated (*cine* S_NAr).

It is important to note at this stage that complex **5** is less reactive than complex **1** because the reaction with **5** requires longer time in order to take place and no *ipso* substitution occurs (yield lower than 1% in the case of complex **7a**).

Treatment of complex **5** with LiCHMeCN (1.2 equiv.) in THF (-78°C, 30 min) and then with CF_3CO_2H (5 equiv.; -78°C, 30 min; r.t., 14 h) affords regioselectively two *meta* diastereoisomers **6b** in 67% yields (Eq. (4)) (*cine* S_NAr). These diastereoisomers obtained in a 36:64 ratio cannot be separated on a silica gel chromatography column.

Treatment of complex **5** with $LiCMe_2CN$ (1.2 equiv.) in THF (-78°C, 30 min) and then with CF_3CO_2H (5 equiv.; -78°C, 30 min; r.t., 4 h) yields complex **6c** in 54% yield (Eq. (4)). A trace of the *para* isomer **7c** (2% yield) can be detected (*tele-meta* S_NAr: same mechanism as in the formation of **15**, Scheme 3). The formation of complexes **6b** and **6c** is easily understood if we consider again an addition of the carbanion on the C3 carbon of the veratrole tricarbonylchromium complex (*cine* S_NAr). The mechanism implies stereospecific hydrogen migrations and MeOH elimination.

We did not succeed in isolating (η^5-cyclohexadienyl)-tricarbonyl chromium hydrides because they are too reactive and we do not know if their best representation is a chromium hydride structure **A** or an (η^4-cyclohexadiene)tricarbonylchromium structure **B** with an agostic hydrogen (Scheme 4) [7c,12]. Nevertheless, elimination of the agostic hydrogen and the leaving group can also interpret the rearomatisation process involved in the last step of the substitution mechanisms described in this work.

4. Conclusions

Addition of stabilised carbanions occurred preferentially on the C5 carbon, eclipsed by a chromium Cr–CO bond, of (η^6-1,2,3-trimethoxybenzene)tricarbonylchromium (**1**). After CF_3CO_2H treatment, *tele-meta* S_NAr takes place and gives 4-substituted veratrole complexes. In the case of veratrole tricarbonylchromium, addition of a stabilised carbanion occurred preferentially on the C3 or C6 carbon. After CF_3CO_2H treatment, *cine* S_NAr gives *meta*-substituted anisole complexes. η^4-Cyclohexadienes and η^5-cyclohexadienyl chromium hydride intermediates explain the isomerisation of these systems in order to facilitate the last step, the elimination of MeOH, which is the driving force of these reactions.

Acknowledgements

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